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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | JUL 20 | Powerful new interactive analysis and visualization software, STN AnaVist, now available |
| NEWS 4 | AUG 11 | STN AnaVist workshops to be held in North America |
| NEWS 5 | AUG 30 | CA/CAplus -Increased access to 19th century research documents |
| NEWS 6 | AUG 30 | CASREACT - Enhanced with displayable reaction conditions |
| NEWS 7 | SEP 09 | ACD predicted properties enhanced in REGISTRY/ZREGISTRY |
| NEWS 8 | OCT 03 | MATHDI removed from STN |
| NEWS 9 | OCT 04 | CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices |
| NEWS 10 | OCT 06 | STN AnaVist workshops to be held in North America |
| NEWS 11 | OCT 13 | New CAS Information Use Policies Effective October 17, 2005 |
| NEWS 12 | OCT 17 | STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools |

| | |
|---|---|
| NEWS EXPRESS | JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005 |
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS INTER | General Internet Information |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS PHONE | Direct Dial and Telecommunication Network Access to STN |
| NEWS WWW | CAS World Wide Web Site (general information) |

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:41:47 ON 18 OCT 2005

=> fil reg
FILE 'REGISTRY' ENTERED AT 12:42:14 ON 18 OCT 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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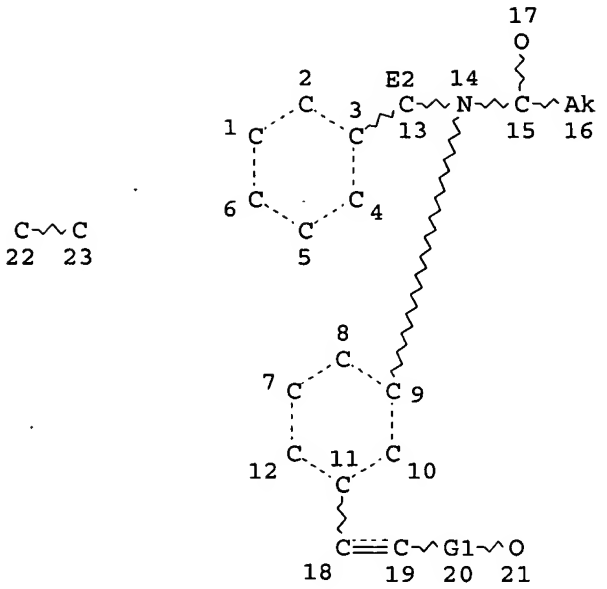
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

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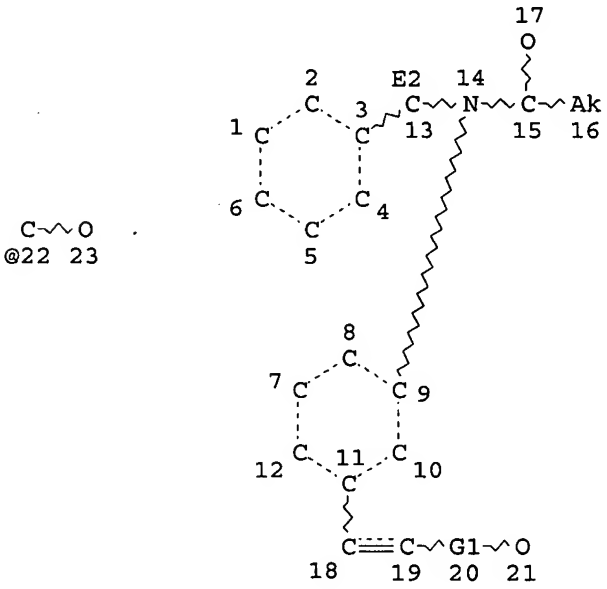


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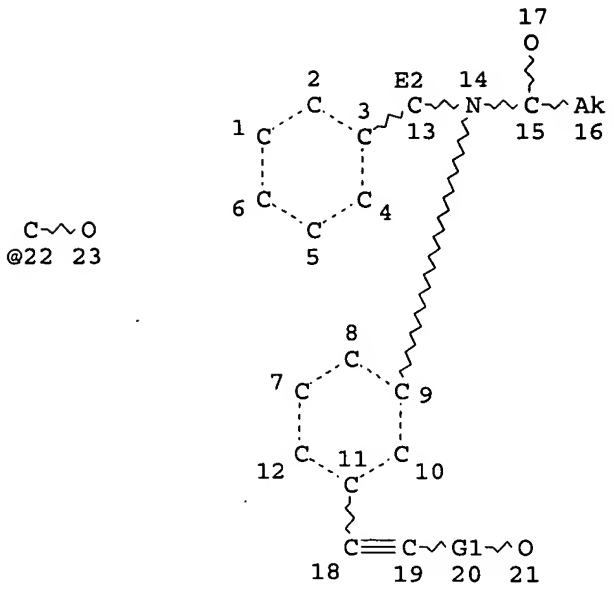
:bon 18-19 t,dis

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L3 STRUCTURE CREATED

=> s l2 or l3
SAMPLE SEARCH INITIATED 12:55:05 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 14 TO ITERATE

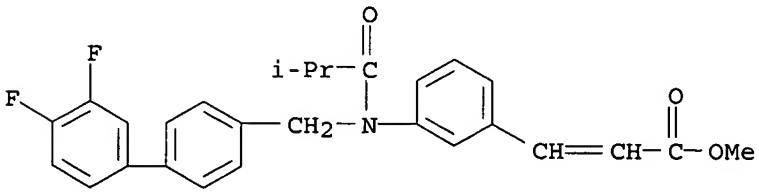
100.0% PROCESSED 14 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 56 TO 504
PROJECTED ANSWERS: 2 TO 124

L4 2 SEA SSS SAM L2 OR L3

=> d scan

L4 2 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Propenoic acid, 3-[3-[[(3',4'-difluoro[1,1'-biphenyl]-4-yl)methyl](2-methyl-1-oxopropyl)amino]phenyl]-, methyl ester (9CI)
MF C27 H25 F2 N O3




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> d l2 or dl3 ful
L2 HAS NO ANSWERS
'OR DL3 FUL ' IS NOT A VALID STRUCTURE FORMAT KEYWORD
Structure Formats
SIA ----- Structure Image, Attributes, and map table if it contains
          data.  (Default)
SIM ----- Structure IMage.
SAT ----- Structure ATtributes and map table if it contains data.
SCT ----- Structure Connection Table and map table if it contains
          data.
SDA ----- All Structure DAta (image, attributes, connection table and
          map table if it contains data).
NOS ----- NO Structure data.
ENTER STRUCTURE FORMAT (SIA), SCT, SDA, SIM, SAT, NOS:end

=> s l2 or l3 ful
FULL SEARCH INITIATED 12:56:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      352 TO ITERATE

100.0% PROCESSED      352 ITERATIONS                              38 ANSWERS
SEARCH TIME: 00.00.01

L5           38 SEA SSS FUL L2 OR L3

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2         RN              699019-78-8  REGISTRY
3         RN              698356-52-4  REGISTRY
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6         RN              698356-35-3  REGISTRY
7         RN              592526-13-1  REGISTRY
8         RN              592526-10-8  REGISTRY
9         RN              592526-08-4  REGISTRY
10        RN              592526-05-1  REGISTRY
11        RN              592526-02-8  REGISTRY
12        RN              592525-99-0  REGISTRY
13        RN              592525-96-7  REGISTRY
14        RN              592525-94-5  REGISTRY
15        RN              592525-91-2  REGISTRY
16        RN              592525-88-7  REGISTRY
17        RN              592525-85-4  REGISTRY
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35        RN              592525-33-2  REGISTRY
36        RN              592525-30-9  REGISTRY
37        RN              574005-64-4  REGISTRY
38        RN              574005-63-3  REGISTRY
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=> d 37 36 1 2 3 sub bib abs

L5 ANSWER 37 OF 38 REGISTRY COPYRIGHT 2005 ACS on STN
RN 574005-64-4 REGISTRY
ED Entered STN: 27 Aug 2003
CN 2-Propenoic acid, 3-[3-[[[4'-(1-methylethyl)[1,1'-biphenyl]-4-yl]methyl](2-methyl-1-oxopropyl)amino]phenyl]-, methyl ester (9CI) (CA INDEX NAME)
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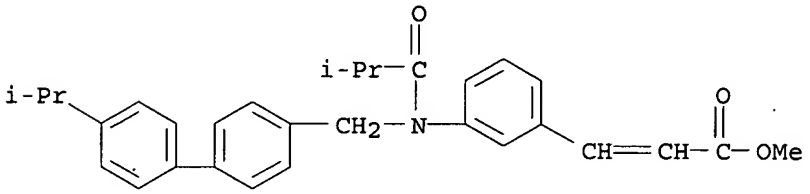
MF C30 H33 N O3
SR CA
LC STN Files: CA, CAPLUS



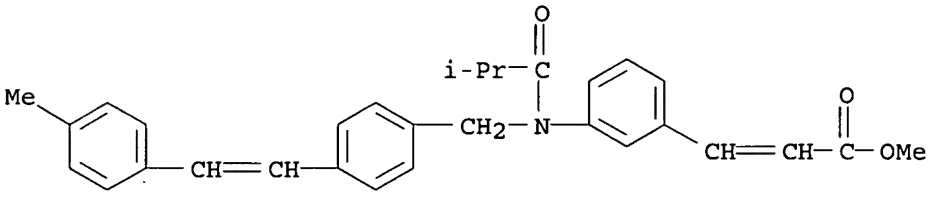

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 139:159454 CA
TI A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR
AU Downes, Michael; Verdecia, Mark A.; Roecker, A. J.; Hughes, Robert; Hogenesch, John B.; Kast-Woelbern, Heidi R.; Bowman, Marianne E.; Ferrer, Jean-Luc; Anisfeld, Andrew M.; Edwards, Peter A.; Rosenfeld, John M.; Alvarez, Jacqueline G. A.; Noel, Joseph P.; Nicolaou, K. C.; Evans, Ronald M.
CS Gene Expression Laboratory, Howard Hughes Medical Institute, La Jolla, CA, 92037, USA
SO Molecular Cell (2003), 11(4), 1079-1092
CODEN: MOCEFL; ISSN: 1097-2765
PB Cell Press
DT Journal
LA English
AB The farnesoid X receptor (FXR) functions as a bile acid (BA) sensor coordinating cholesterol metabolism, lipid homeostasis, and absorption of dietary fats and vitamins. However, BAs are poor reagents for characterizing FXR functions due to multiple receptor independent properties. Accordingly, using combinatorial chemical we evolved a small mol. agonist termed fexaramine with 100-fold increased affinity relative to natural compds. Gene-profiling expts. conducted in hepatocytes with FXR-specific fexaramine vs. the primary BA chenodeoxycholic acid (CDCA) produced remarkably distinct genomic targets. Highly diffracting cocrystals (1.78 Å) of fexaramine bound to the ligand binding domain of FXR revealed the agonist sequestered in a 726 Å3 hydrophobic cavity and suggest a mechanistic basis for the initial step in the BA signaling pathway. The discovery of fexaramine will allow us to unravel the FXR genetic network from the BA network and selectively manipulate components of the cholesterol pathway that may be useful in treating cholesterol-related human diseases.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 36 OF 38 REGISTRY COPYRIGHT 2005 ACS on STN
RN 592525-30-9 REGISTRY
ED Entered STN: 25 Sep 2003
CN 2-Propenoic acid, 3-[3-[(2-methyl-1-oxopropyl)[[4-[2-(4-methylphenyl)ethenyl]phenyl]methyl]amino]phenyl]-, methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C30 H31 N O3
SR CA
LC STN Files: CA, CAPLUS, USPATFULL




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 141:23422 CA
TI Preparation of non-steroidal FXR agonists
IN Nicolaou, Kyriacos C.; Roecker, Anthony J.; Hughes, Robert; Pfefferkorn, Jeffrey A.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004046162 | A2 | 20040603 | WO 2003-US36195 | 20031114 |
| | WO 2004046162 | A3 | 20040812 | | |
| | WO 2004046162 | C1 | 20050324 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-426456P 20021114
US 2003-491185P 20030729
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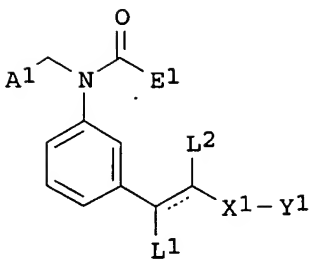


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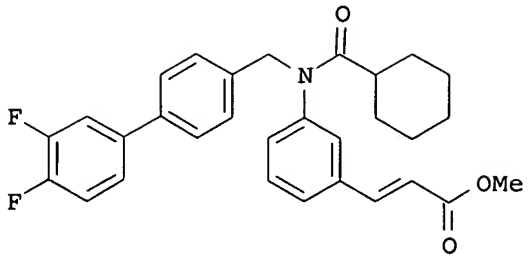


II

AB Non-steroidal N-aryl-N-arylmethyl amido and ureido compds. such as I [E1 = (C1-C8)alkyl, cyclohexyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, Ph, NH(C1-C8)alkyl; L1, L2 = H; dashed bond = single bond or double bond; X1 = CO, CH2; Y1 = H, NHZ1, NH(Z2)Z3, OZ4; A1 = aryl, heterocyclyl etc.; Z1 = H, Ph, alkyl, benzyl, benzoyl; Z2, Z3 = alkyl; Z2Z3 = cycloalkyl; Z4 = H, oxygen protecting group], were prepared for their therapeutic use as farnesoid X receptor (FXR) agonists. Thus, biaryl compound II, prepared via solid phase synthesis starting from N-(tert-butoxycarbonyl)-3-aminocinnamic acid, Merrifield Resin, 4-bromobenzaldehyde, cyclohexanoyl chloride, and 3,4-difluorobenzeneboronic acid, showed FXR activity (EC50 = 72 nM) and relative efficacy = 1.70 at 1-100 mM CDCA from a cell-based assay. The FXR agonists are useful as therapeutic agents for the treatment of diseases linked to cholesterol, bile acids, and their metabolism and homeostasis.

REFERENCE 2

AN 141:17647 CA
TI N-acyl-N-arylmethylaniline acrylates as nonsteroidal farnesoid X receptor modulators
IN Downes, Michael R.; Evans, Ronald M.
PA The Salk Institute for Biological Studies, USA
SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004046068 | A2 | 20040603 | WO 2003-US36137 | 20031114 |
| | WO 2004046068 | A3 | 20041229 | | |
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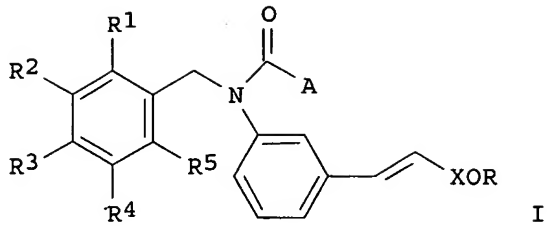
| | RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 2005143449 | A1 | 20050630 | US 2003-658115 | 20030908 |
| PRAI | US 2002-426664P | | 20021115 | | |
| | US 2003-658115 | | 20030908 | | |

GI

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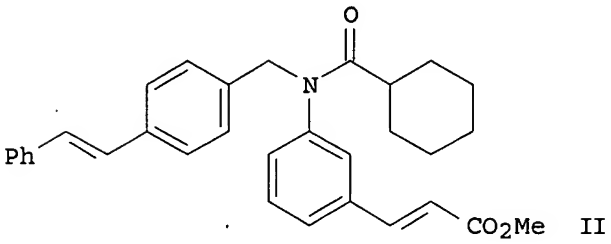


II

AB A method for modulating process(es) mediated by farnesyl X receptor polypeptides comprises conducting said process(es) in the presence of title compds. [I; A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH2; R = Me, Et; R1 = H, OH, alkoxy, PhCO2, mesityloxy, OCH2CO2Et; R2 = H; R3 = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R2R3 = atoms to form a (substituted) (unsatd.) pyran ring; R4 = H, OH; R5 = H, OH, alkoxy, aryloxy]. In a cell-based transcription assay, title compound (II) activated FXR with EC50 = 36 nM.

REFERENCE 3

AN 141:17646 CA
TI N-acyl-N-benzylaniline acrylates as nonsteroidal farnesoid X receptor (FXR) modulators
IN Downes, Michael R.; Evans, Ronald Mark; Hughes, Robert; Nicolaou, Kyriacos C.; Roecker, Anthony J.
PA The Salk Institute for Biological Studies, USA; The Scripps Research Institute
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004045511 | A2 | 20040603 | WO 2003-US36123 | 20031114 |
| | WO 2004045511 | A3 | 20040708 | | |
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| | RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 2005143449 | A1 | 20050630 | US 2003-658115 | 20030908 |
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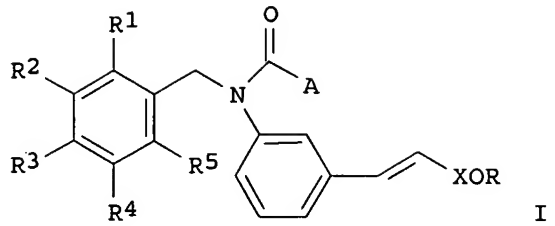


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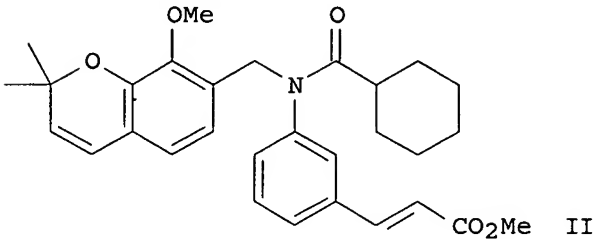


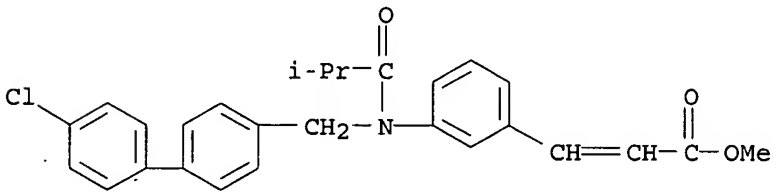

II

AB Title compds. [I; A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH2; R = Me, Et; R1 = H, OH, alkoxy, PhCO2, mesityloxy, OCH2CO2Et; R2 = H; R3 = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R2R3 = atoms to form a substituted (unsatd.) pyran ring; R4 = H, OH; R5 = H, OH, alkoxy, aryloxy], are claimed. Thus, benzopyran derivative (II) activated FXR receptors with EC50 = 358 nM.

REFERENCE 4

AN 139:224366 CA
TI Discovery and optimization of non-steroidal FXR agonists from natural product-like libraries
AU Nicolaou, K. C.; Evans, Ronald M.; Roecker, A. J.; Hughes, Robert; Downes, Michael; Pfefferkorn, Jeffery A.
CS Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Organic & Biomolecular Chemistry (2003), 1(6), 908-920
CODEN: OBCRAK; ISSN: 1477-0520
PB Royal Society of Chemistry
DT Journal
LA English
AB The efficient regulation of cholesterol biosynthesis, metabolism, acquisition, and transport is an essential component of lipid homeostasis. The farnesoid X receptor (FXR) is a transcriptional sensor for bile acids, the primary product of cholesterol metabolism Accordingly, the development of potent, selective, small mol. agonists, partial agonists, and antagonists of FXR would be an important step in further deconvoluting FXR physiol. Herein, we describe the development of four novel classes of potent FXR activators originating from natural product-like libraries. Initial screening of a 10000-membered, diversity-orientated library of benzopyran containing small mols. for FXR activation utilizing a cell-based reporter assay led to the identification of several lead compds. possessing low micromolar activity (EC50's = 5-10 μM). These compds. were systematically optimized employing parallel solution-phase synthesis and solid-phase synthesis to provide four classes of compds. that potently activate FXR. Two series of compds., bearing stilbene or biaryl moieties, contain members that are the most potent FXR agonists reported to date in cell-based assays. These compds. may find future utility as chemical tools in studies aimed at further defining the physiol. role of FXR and discovering potential therapeutic agents for the treatment of diseases linked to cholesterol and bile acid metabolism and homeostasis.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 1 OF 38 REGISTRY COPYRIGHT 2005 ACS on STN
RN 858360-31-3 REGISTRY
ED Entered STN: 04 Aug 2005
CN 2-Propenoic acid, 3-[3-[[(4'-chloro[1,1'-biphenyl]-4-yl)methyl](2-methyl-1-oxopropyl)amino]phenyl]-, methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C27 H26 Cl N O3
SR CA
LC STN Files: CA, CAPLUS



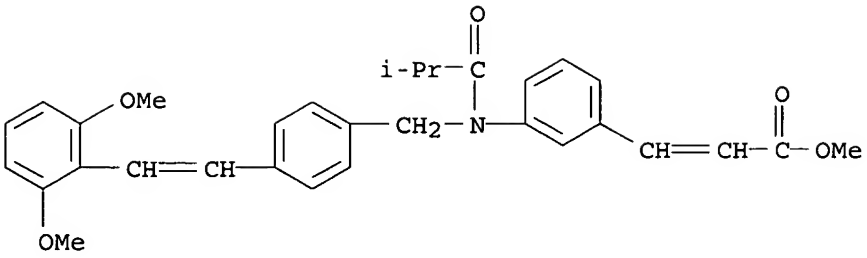
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 143:125843 CA
TI Hologram quantitative structure-activity relationships for a series of farnesoid X receptor activators
AU Honorio, Kathia M.; Garratt, Richard C.; Andricopulo, Adriano D.
CS Instituto de Fisica de Sao Carlos, Centro de Biotecnologia Molecular Estrutural, Laboratorio de Quimica Medicinal e Computacional, Universidade de Sao Paulo, Sao Carlos-SP, 13560-970, Brazil
SO Bioorganic & Medicinal Chemistry Letters (2005), 15(12), 3119-3125
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier B.V.
DT Journal
LA English
AB The farnesoid X receptor (FXR) is an attractive drug target for the development of novel therapeutic agents for the treatment of dyslipidemia and cholestasis. Hologram quant. structure-activity relationship (HQSAR) studies were conducted on a series of potent FXR activators originated from natural product-like libraries. A training set containing 82 compds. served to establish the models. The best HQSAR model was generated using atoms, bonds, connections, chirality, and donor and acceptor as fragment distinction and fragment size default (4-7) with six components. The model was used to predict the potency of 20 test set compds. that were not included in the training set, and the predicted values were in good agreement with the exptl. results. The final HQSAR model and the information obtained from HQSAR 2D contribution maps should be useful for the design of novel FXR ligands having improved potency.
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 38 REGISTRY COPYRIGHT 2005 ACS on STN
RN 699019-78-8 REGISTRY
ED Entered STN: 25 Jun 2004
CN 2-Propenoic acid, 3-[3-[[[4-[2-(2,6-dimethoxyphenyl)ethenyl]phenyl]methyl](2-methyl-1-oxopropyl)amino]phenyl]-, methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H33 N O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 141:17646 CA
TI N-acyl-N-benzylaniline acrylates as nonsteroidal farnesoid X receptor (FXR) modulators
IN Downes, Michael R.; Evans, Ronald Mark; Hughes, Robert; Nicolaou, Kyriacos C.; Roecker, Anthony J.
PA The Salk Institute for Biological Studies, USA; The Scripps Research Institute
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004045511 | A2 | 20040603 | WO 2003-US36123 | 20031114 |
| | WO 2004045511 | A3 | 20040708 | | |
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| | RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 2005143449 | A1 | 20050630 | US 2003-658115 | 20030908 |
| PRAI | US 2002-426664P | | 20021115 | | |
| | US 2003-658115 | | 20030908 | | |

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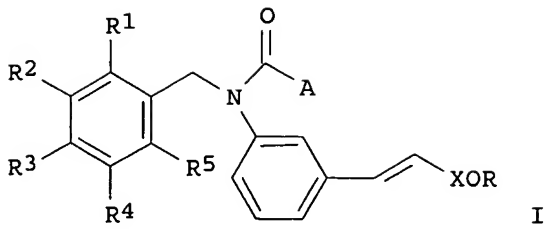

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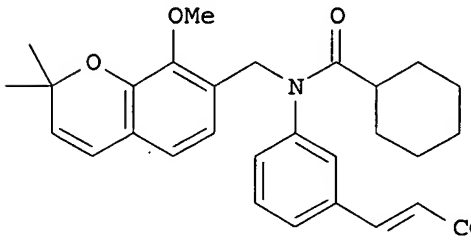
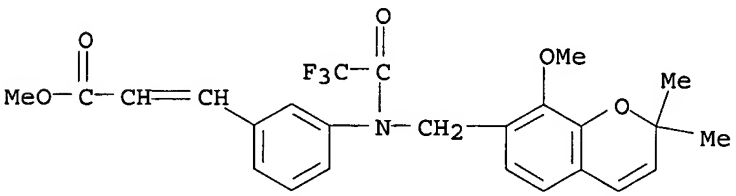


II

AB Title compds. [I; A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH2; R = Me, Et; R1 = H, OH, alkoxy, PhCO2, mesityloxy, OCH2CO2Et; R2 = H; R3 = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R2R3 = atoms to form a substituted (unsatd.) pyran ring; R4 = H, OH; R5 = H, OH, alkoxy, aryloxy], are claimed. Thus, benzopyran derivative (II) activated FXR receptors with EC50 = 358 nM.

L5 ANSWER 3 OF 38 REGISTRY COPYRIGHT 2005 ACS on STN
RN 698356-52-4 REGISTRY
ED Entered STN: 24 Jun 2004
CN 2-Propenoic acid, 3-[3-[[(8-methoxy-2,2-dimethyl-2H-1-benzopyran-7-yl)methyl](trifluoroacetyl)amino]phenyl]-, methyl ester (9CI) (CA INDEX NAME)
MF C25 H24 F3 N O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1

AN 141:23422 CA
TI Preparation of non-steroidal FXR agonists
IN Nicolaou, Kyriacos C.; Roecker, Anthony J.; Hughes, Robert; Pfefferkorn, Jeffrey A.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004046162 | A2 | 20040603 | WO 2003-US36195 | 20031114 |
| | WO 2004046162 | A3 | 20040812 | | |
| | WO 2004046162 | C1 | 20050324 | | |

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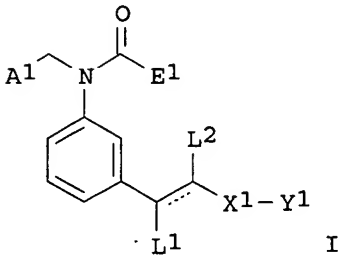
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-426456P 20021114
US 2003-491185P 20030729

GI

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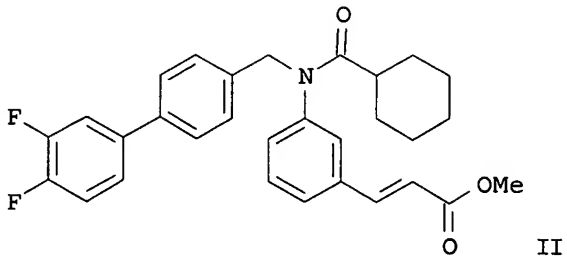


II

AB Non-steroidal N-aryl-N-arylmethyl amido and ureido compds. such as I [E1 = (C1-C8)alkyl, cyclohexyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, Ph, NH(C1-C8)alkyl; L1, L2 = H; dashed bond = single bond or double bond; X1 = CO, CH2; Y1 = H, NHZ1, NH(Z2)Z3, OZ4; A1 = aryl, heterocyclyl etc.; Z1 = H, Ph, alkyl, benzyl, benzoyl; Z2, Z3 = alkyl; Z2Z3 = cycloalkyl; Z4 = H, oxygen protecting group], were prepared for their therapeutic use as farnesoid X receptor (FXR) agonists. Thus, biaryl compound II, prepared via solid phase synthesis starting from N-(tert-butoxycarbonyl)-3-aminocinnamic acid, Merrifield Resin, 4-bromobenzaldehyde, cyclohexanoyl chloride, and 3,4-difluorobenzeneboronic acid, showed FXR activity (EC50 = 72 nM) and relative efficacy = 1.70 at 1-100 mM CDCA from a cell-based assay. The FXR agonists are useful as therapeutic agents for the treatment of diseases linked to cholesterol, bile acids, and their metabolism and homeostasis.

REFERENCE 2

AN 141:17647 CA
TI N-acyl-N-arylmethylaniline acrylates as nonsteroidal farnesoid X receptor modulators
IN Downes, Michael R.; Evans, Ronald M.
PA The Salk Institute for Biological Studies, USA
SO PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2004046068 | A2 | 20040603 | WO 2003-US36137 | 20031114 |
| | WO 2004046068 | A3 | 20041229 | | |

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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005143449 A1 20050630 US 2003-658115 20030908

PRAI US 2002-426664P 20021115
US 2003-658115 20030908

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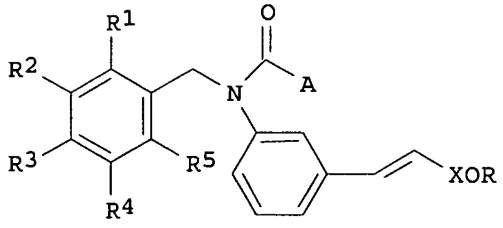


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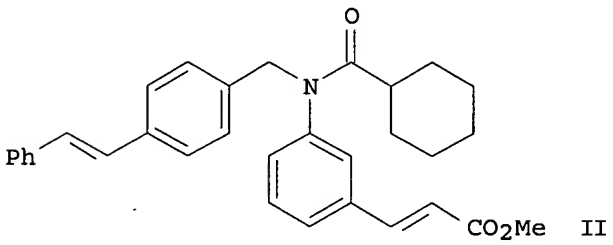


II

AB A method for modulating process(es) mediated by farnesyl X receptor polypeptides comprises conducting said process(es) in the presence of title compds. [I; A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH2; R = Me, Et; R1 = H, OH, alkoxy, PhCO2, mesityloxy, OCH2CO2Et; R2 = H; R3 = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R2R3 = atoms to form a (substituted) (unsatd.) pyran ring; R4 = H, OH; R5 = H, OH, alkoxy, aryloxy]. In a cell-based transcription assay, title compound (II) activated FXR with EC50 = 36 nM.

REFERENCE 3

AN 141:17646 CA

TI N-acyl-N-benzylaniline acrylates as nonsteroidal farnesoid X receptor (FXR) modulators

IN Downes, Michael R.; Evans, Ronald Mark; Hughes, Robert; Nicolaou, Kyriacos C.; Roecker, Anthony J.

PA The Salk Institute for Biological Studies, USA; The Scripps Research Institute

SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2004045511 | A2 | 20040603 | WO 2003-US36123 | 20031114 |

WO 2004045511 A3 20040708
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2005143449 A1 20050630 US 2003-658115 20030908
PRAI US 2002-426664P 20021115
US 2003-658115 20030908
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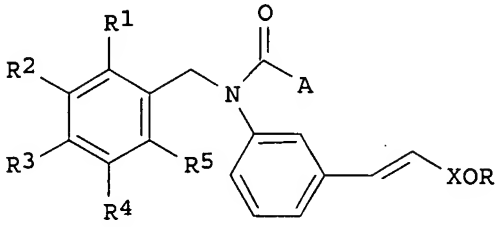

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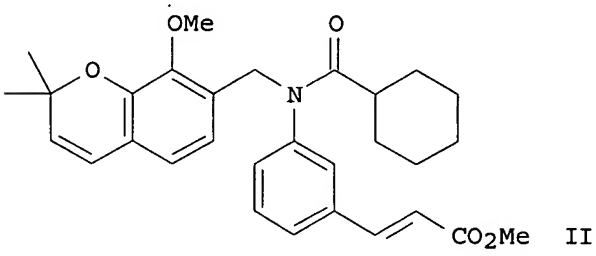

II

AB Title compds. [I; A = (substituted) alkyl, cycloalkyl, aryl, heteroaryl; X = CO, CH2; R = Me, Et; R1 = H, OH, alkoxy, PhCO2, mesityloxy, OCH2CO2Et; R2 = H; R3 = alkenyl, (substituted) aryl, heteroaryl, aralkenyl, heteroaralkenyl; R2R3 = atoms to form a substituted (unsatd.) pyran ring; R4 = H, OH; R5 = H, OH, alkoxy, aryloxy], are claimed. Thus, benzopyran derivative (II) activated FXR receptors with EC50 = 358 nM.

=> log h

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 289.04 | 289.25 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -3.40 | -3.40 |

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 13:01:59 ON 18 OCT 2005